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CLINICOPATHOLOGICAL OUTCOME OF RADICAL RETROPUBIC PROSTATECTOMY FOR 200 MEN WITH PROSTATE CANCER IN A SINGLE INSTITUTION IN JAPAN

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The objective of this study was to retrospectively evaluate the clinicopathological outcome of radical retropubic prostatectomy (RRP) performed at a single institution in Japan. A consecutive series of 200 patients with prostate cancer who underwent RRP and pelvic lymphadenectomy between March 1985 and April 2003 were included in this study. The median age at RRP and the observation period were 69 years old and 43 months, respectively. Clinicopathological findings were reviewed to determine parameters providing predictive information about biochemical recurrence-free, cause-specific, and overall survivals. The pathological stage was pT0 in 7 patients (3.5%), pT2a in 43 (21.5%), pT2b in 58 (29.0%), pT3a in 42 (21.0%) pT3b in 36 (18.0%), and pT4 in 14 (7.0%). Lymph node metastasis was detacted in 32 of 200 patients (16.0%). Forty-seven patients (23.5%) received neoadjuvant hormonal therapy, while 48 (24.0%) underwent hormonal therapy alone or hormonal therapy plus radiotherapy following RRP as an adjuvant treatment. During the observation period, 4 patients (2.0%) died of prostate cancer, 11 (5.5%) died of other diseases and biochemical recurrence occurred in 23 (11.5%), when biochemical recurrence was defined as prostate specific antigen (PSA) persistently greater than 0.4 ng/ml. Five-year biochemical recurrence-free, cause-specific, and overall survival rates were 83.6%, 97.7% and 91.4%, respectively. Furthermore, multivariate analyses showed that lymph node metastasis or clinical stage was an independent predictive factor for cause-specific or overall survival, respectively. These findings suggest that it would be possible to achieve a favorable cancer control for patients with localized prostate cancer, including locally advanced cases, by the RRP-based combination therapies.

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Key words : Prostate cancer, Radical retropubic prostatectomy, Prognosis

INTRODUCTION

Recent understanding of periprostatic anatomy has improved the outcome of radical retropubic prostatectomy (RRP)[1] In 1983, Walsh et al., introduced a refined technique for RRP, which requires the prostate removed with controlled hemostasis, resulting in adequate visualization of the periprostatic anatomy, such as the urethral sphincter, neurovascular bundles, and dorsal vein complex[2] With this procedure, sexual function and urinary continence can be preserved, and surgical mortality rates have been reduced to less than 0.5%. Improved outcome associated with the modification of surgical techniques has resulted in greater general acceptance of this treatment[3–5]

Consistent with Western industrialized countries, RRP has become more widely used among Japanese urologists over the last decade. Furthermore, since increased screening for prostate cancer using prostate-specific antigen (PSA) has led to an apparent increase in the detection of prostate cancer at a lower tumor stage, the number of patients undergoing RRP continues to increase markedly[6]. However, there have been few studies concerning the outcome of RRP performed in a Japanese institution; therefore, we retrospectively analyzed the clinicopathological data for 200 patients with prostate cancer who underwent RRP at our institution.

PATIENTS AND METHODS

This study includes a consecutive series of 200 patients with prostate cancer who underwent radical retropubic prostatectomy after histopathological diagnosis of prostate cancer by systematic transrectal ultrasound-guided needle biopsy and/or transurethral resection of the prostate in our institution between March 1985 and April 2003. With time, we modified the surgical technique incorporating our experience and the findings reported in the urological literature, As a rule, however, we used the surgical technique described by Walsh et al.[2], and modified by others[7–9], with one exception; that is, the neurovascular bundles on the cancer side were routinely

sacrificed. Generally, bilateral pelvic lymphadenectomy targeting the external iliac, internal iliac and obturator lymph nodes were performed. However, only obturator lymph nodes were dissected in 20 of these 200 patients.

Clinical staging usually was done by digital rectal examination, radioisotope bone scanning, and abdominal and pelvic computerized tomography (CT). The resected prostatectomy specimens were fixed and whole-mount step sections were cut transversely at 5-mm intervals from the apex of the prostate to the tips of the seminal vesicles. Each section was examined for cancer location, capsular penetration, and seminal vesicle invasion. Both the clinical and pathological stages were determined according to the UICC (TNM) tumor stage classification[10] In addition, since the Gleason grading system was not adopted until 1993 at our institution, we graded tumors according to a modification of the Gleason grading system used as well (Gleason score 2–4), moderately (Gleason score 5–7), or poorly (Gleason score 8–10) differentiated[1]

Among these 200 patients, neoadjuvant hormonal therapy was administered to 47 patients (23.5%), who were likely to have locally advanced disease judging from several clinical examinations, such as biopsy findings, serum PSA values, and CT findings. As neoadjuvant hormonal therapy, bilateral orchiectomy was performed in 3 patients, luteinizing hormone-releasing hormone (LH-RH) analogue was administered in 18, and the remaining 26 underwent total androgen blockade consisting of LH-RH analogue and antiandrogen. In this series, as a rule, neoadjuvant hormonal therapy was continuously performed for at least 8 months (median : 12 months ; range : 3–98 months).

Currently, we do not perform any adjuvant therapies, even in patients with pathological risk factors for recurrence, such as extracapsular penetration and lymph node metastasis. However, between 1988 and 1996, 38 patients with extraprostatic disease received hormonal therapy plus pelvic radiotherapy as adjuvant treatments. Either bilateral orchiectomy or LH-RH and analogue was selected according to the patient as an adjuvant hormonal therapy. The median dose for adjuvant radiation was 60 Gray (range : 45–68 Gray) in 2 Gray fractions in the whole pelvis.

We usually followed the patients by periodical measurement of serum PSA values (Tosoh, Tokyo, Japan), and the measurement interval was determined in consideration of the potential risk of recurrence in each patient. Biochemical recurrence was defined as PSA persistently greater than 0.4 ng/ml. Post-recurrence treatment included hormonal therapy alone or hormonal therapy plus pelvic radiotherapy as described above.

Differences between the two groups were compared using the chi-squared test or unpaired t test. Survival rates were calculated by the Kaplan-Meier method, and the difference was determined by the log rank test. The prognostic significance of some factors was assessed by the multivariate Cox proportional hazards regression model. P values <0.05 were considered significant.

RESULTS

Characteristics of 200 patients included in the present study are summarized in Table 1. We then analyzed the distribution of pretreatment PSA, tumor grade, and lymph node metastasis according to the pathological stage. As shown in Table 2, these three factors were significantly associated with pathological stage.

In this series, 111 patients (55.5%) received RRP alone, 41 (20.5%) RRP and neoadjuvant hormonal therapy, 42 (21.0%) RRP and adjuvant therapy, and 6 (3.0%) RRP and neoadjuvant hormonal therapy plus adjuvant therapy. The effects of different treatments on the incidence of biochemical recurrence were subsequently evaluated. Althogh the patients receiving adjuvant therapy tended to be distributed in higher pathological stages, the incidence of

Table 1. Patient characteristics

No. of patients	200
Median age at prostatectomy (year, range)	69 (45–82)
Median observation period (month)	43 (8–212)
Pretreatment median PSA (ng/ml, range)	10.1 (0.6–408)
Clinical stage (%) :	
T1a	2 (1.0)
T1b	11 (5.5)
T1c	52 (26.0)
T2a	80 (40.0)
T2b	35 (17.5)
T3a	9 (4.5)
T3b	6 (3.0)
T4	5 (2.5)
Pathological stage (%) :	
pT0	7 (3.5)
pT2a	43 (21.5)
pT2b	58 (29.0)
pT3a	42 (21.0)
pT3b	36 (18.0)
pT4	14 (7.0)
Tumor grade (%) :	
No residual tumor	7 (3.5)
Well differentiated	48 (24.0)
Moderately differentiated	111 (55.5)
Poorly differentiated	34 (17.0)
Lymph node metastasis (%) :	
pN0	168 (84.0)
pN1	32 (16.0)

Table 2. Clinicopathological findings according to pathological stage

Pathological stage	Pretreatment PSA (ng/ml)				Tumor grade			Lymph node metastasis	
	0–3.9	4–9.9	10–19.9	20 or greater	Well differentiated	Moderately differentiated	Poorly differentiated	pN0	pN1
pT0	1	3	1	2	—	—	—	7	0
pT2	18	53	16	14	39	54	8	99	2
pT3	0	25	29	24	8	53	17	57	21
pT4	0	0	1	13	1	4	9	5	9
Total	19	81	47	53	48	111	34	168	32

Table 3. Incidence of biochemical recurrence according to additive treatment to prostatectomy

Treatment	No. of patients with biochemical recurrence/Total No. of patients				
	Pathological stage				
	pT0	pT2a	pT2b	pT3a	Total
Prostatectomy alone	0/1	7/75	6/32	1/3	14/111
Prostatectomy+ Neoadjuvant therapy	0/6	2/21	2/ 9	1/5	5/ 41
Prostatectomy+ Adjuvant therapy	0/0	0/ 5	2/34	1/3	3/ 42
Prostatectomy+ Neoadjuvant and Adjuvant therapies	0/0	0/ 0	0/ 3	1/3	1/ 6

biochemical recurrence was almost similar to that in patients undergoing RRP alone or RRP plus neoadjuvant hormonal therapy (Table 3).

During the observation period in this study, only 4 (2%) patients died of progression of prostate cancer, and 11 (5.5%) died of other diseases. Biochemical recurrence was observed in 23 patients (11.5%), when it was defined as PSA persistently greater than 0.4 ng/ml. As shown in Table 4, 5-year biochemical recurrence-free, cause-specific, and overall survival rates were 83.6%, 97.7%, and 91.4%, respectively. Multivariate Cox regression analyses were then performed to determine the parameters that provide predictive information about the biochemical recurrence-free, cause-specific, and overall survivals. None of the factors we examined could be an independent predictor of biochemical recurrence; however, lymph node metastasis or clinical stage was an independent predictive factor for cause-specific or overall survival, respectively.

Table 4. Survival rates after radical retropubic prostatectomy

End point	Survival rates (%)			
	1-year	3-years	5-years	10-years
Biochemical recurrence-free survival	91.3	86.2	83.6	81.5
Cancer specific survival	100	99.1	97.7	94.6
Overall survival	99.5	97.7	91.4	80.3

DISCUSSION

Over the past 20 years, accumulated anatomic discoveries have improved the ability of urologists to remove the tumor completely by RRP and has markedly reduced postoperative morbidity as well as mortality[1] For example, clasification of the anatomy of the dorsal vein complex improved hemostasis and allowed precise dissection in a relatively bloodless field. With the exact understanding of the anatomy of the pelvic plexus and its

Table 5. Multivariate analysis of clinicopathological factors as prognostic indicators

Variables	Biochemical recurrence-free survival		Cancer-specific survival		Overall survival	
	Relative risk (95% confidence interval)	P value	Relative risk (95% confidence interval)	P value	Relative risk (95% confidence interval)	P value
Age at prostatectomy (years) (<70 versus 70≦)	0.856 (0.378–1.936)	0.709	0.263 (0.022– 3.163)	0.292	0.639 (0.216– 1.887)	0.417
Pretreatment PSA (ng/ml) (<10 versus 10≦)	0.823 (0.323–2.098)	0.683	0.835 (0.064– 10.941)	0.891	0.770 (0.174– 3.402)	0.730
Clinical stage (≦T1c versus T2a≦)	0.786 (0.252–2.446)	0.677	22.129 (0.936–523.178)	0.055	4.809 (1.259–18.372)	0.022
Pathological stage (≦T2b versus T3a≦)	0.795 (0.276–2.291)	0.671	0.201 (0.009– 4.653)	0.317	1.368 (0.293– 6.391)	0.690
Tumor grade (well or moderately differentiated versus poorly differentiated)	1.050 (0.377–2.927)	0.925	3.535 (0.311– 40.245)	0.309	1.508 (0.346– 6.571)	0.584
Lymph node metastasis (pN0 versus pN1)	0.664 (0.238–1.857)	0.435	0.044 (0.003– 0.740)	0.030	0.274 (0.073– 1.024)	0.054

branches to the corpora cavernosa, modified surgical techniques have made it possible to preserve sexual function. With such advances, RRP has become the gold standard in the management of localized prostate cancer[7]. In Japan as well, the incidence of prostate cancer has drastically increased, particularly the number of cancers detected early and which could be candidates for surgical therapy has increased, thus resulting in the increased number of RRP performed by Japanese urologists[6]. However, to date, few studies have been reported concerning the outcome of RRP in a large number of patents in Japan. We, therefore, retrospectively analyzed the clinicopathological outcome of a consecutive series of 200 patients with prostate cancer who underwent RRP at a single institution in Japan.

In this series, we generally followed the well established methods for perioperative management of prostate cancer patients, with some exceptions: 1) The neurovascular bundles on the cancer side were routinely sacrificed. 2) Neoadjuvant hormonal therapy was performed for at least 8 months in those who were clinically diagnosed as having locally advanced disease. 3) In the early series, hormonal therapy plus pelvic radiation was performed following RRP as an adjuvant therapy for patients with pathologically confirmed extraprostatic disease. Furthermore, some other details of the method we used have gradually changed with time. Although it would be difficult to draw definitive overall conclusions by analyzing these 200 patients, we obtained several important findings.

This series seems to contain a typical patient population judging from their clinicopathological characteristics. In addition, the pathological stage was significantly correlated to pretreatment PSA values, tumor grade, and lymph node metastasis consistent with previous reports[1,3–5] These findings support the optimal patient selection as well as surgical procedures in our institution. As described above, the patients included in this series underwent various kinds of combined therapy, resulting in different effects on biochemical recurrence. For example, neoadjuvant hormonal therapy prior to RRP may influence the results of biochemical recurrence. Because several previous studies failed to demonstrate prognostic benefit of neoadjuvant hormonal therapy for 3 months targeting clinically organ-confined disease[11,12], we performed neoadjuvant hormonal therapy for at least 8 months on patients who were likely to have locally advanced disease. In addition, the biochemical recurrence-free survival rates in the patients who received adjuvant therapy, mostly consisting of combined hormonal therapy and radiation, were similar to those in the patients not receiving adjuvant therapy, despite their relatively higher pathological stage. However, our prognostic evaluation also suggested that an appropriate therapeutic strategy after biochemical recurrence could protect patients without adjuvant therapy from cancer-specific death, considering the extremely high cancer-specific survival rate. Therefore, recently we do not perform any adjuvant therapies, even in patients with pathological risk factors.

In our series, cancer control results of patients undergoing RRP were within the confidence range of survival rates reported from the academic prostate cancer treatment centers in United States[1,4,13,14], although some investigators have implied that good cancer cure rates can be expected only at high volume academic centers, where surgeons perform several hundred RRP yearly. The multivariate Cox proportional hazards models showed that lymph node metastasis or clinical stage was an independent predictive factor for cause-specific or overall survival, respectively, while none of the factors we examined could be an independent predictor of biochemical recurrence. These results might be due to the lack of uniformity of therapeutic strategy. For example, a powerful inhibitory effect of the adjuvant treatment on biochemical recurrence might confound the statistical analysis, and typical predictors of biochemical recurrence, such as pretreatment PSA, tumor grade, pathological stage, failed to be recognized as independent factors.

In conclusion, our retrospective study at a single institution in Japan suggested that it would be possible to achieve a favorable disease control for patients with localized prostate cancer, including locally advanced cases, by RRP-based combination therapies.

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和文抄録

根治的恥骨後式前立腺全摘除術を施行した200症例の臨床病理学的検討

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兵庫県立成人病センター開設以来，前立腺癌に対して根治的恥骨後式前立腺全摘除術を施行した200症例の臨床病理学的検討を行った．臨床的に局所進行性病変の存在が疑われた症例に対しては，原則的に，8カ月以上の術前内分泌療法を施行した後に前立腺全摘除術を施行した．年令は45～82歳（中央値69歳），観察期間は8～212カ月（中央値43カ月），治療前 PSA 値は 0.6～408 ng/ml（中央値 10.1 ng/ml）であった．臨床病期の内訳は，T1a 2例（1.0%），T1b 11例（5.5%），T1c 52例（26.0%），T2a 80例（40.0%），T2b 35例（17.5%），T3a 9例（4.5%），T3b 6例（3.0%）および T4 5例（2.5%）であった．術前内分泌療法は47例（23.5%）に対して施行され，その期間は3～98カ月（中央値12カ月）であった．病理学的病期は pT0 7例（3.5%），pT2a 43例（21.5%），pT2b 58例（29.0%），pT3a 42例（21.0%），pT3b 36例（18.0%）および pT4 14例（7.0%）で，リンパ節転移は32例（16.0%）に認めた．また，48例（24.0%）に何らかの術後補助療法が施行されていた．経過観察期間中に，癌死4例および他因死11例を認めた．また，生化学的再発を PSA >0.4 ng/ml と定義すると，この間に23例（11.5%）に生化学的再発を認めた．5年生化学的非再発率，疾患特異的生存率および全生存率は，それぞれ83.6，97.7%および91.4%であった．多変量解析の結果，リンパ節転移の有無および臨床病期が，それぞれ疾患特異的生存率および全生存率の独立した予後規定因子であった．以上より，局所進行性症例を含む手術可能な前立腺癌症例に対し，根治的前立腺全摘除術を中心とした治療により良好な長期予後がえられることが示唆された．

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